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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Tulin Morcol, et al.

SERIAL NO.: 09/932,503 GROUP ART UNIT: 1645

FILED: 08/17/2001 EXAMINER: Zeman, Robert A.

FOR: COMPOSITIONS AND METHODS FOR THERAPEUTIC AGENTS COMPLEXED WITH CALCIUM PHOSPHATE AND ENCASED BY CASEIN

ATTORNEY DOCKET NO.: 37070/207071
DATE: May 16, 2005

Commissioner for Patents
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Sandee Whitley

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AMENDMENT AND RESPONSE UNDER 37 C.F.R. §1.116

Sir or Madam:

In response to the Office Action of January 14, 2005, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims that begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

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May 16, 2005

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Examiner Robert A. Zeman 571-272-0866	703-872-9306	U.S. Patent & Trademark Office Alexandria, Virginia

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COMMENTS

The "RECEIVED" stamp on the card acknowledges receipt of the enclosed:

Applicants: Tulin MORCOL, et al.
Title: "Compositions and Methods for Therapeutic Agents Complexed with Calcium Phosphate and Encased by Casein"
Serial No. 09/932,503 Docket No. 37070/207071 Filed Aug. 17, 2001

1. Transmittal Form (PTO/SB/21)
2. Amendment And Response To Office Action And Petition For Extension of Time
3. Credit Card Payment Form

Date: May 16, 2005
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission: 12

Application Number	09/932,503
Filing Date	August 17, 2001
First Named Inventor	Tulin Morcol
Art Unit	1645
Examiner Name	Zeman, Robert
Attorney Docket Number	37070/207071

ENCLOSURES *(check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☒ Amendment / Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☒ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
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- ☐ Petition to Convert to a Provisional Application
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Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm	Kilpatrick Stockton LLP		
Signature	Kristin Gall		
Printed Name	Kristin M. Clall		
Date	May 16, 2005	Reg. No.	48,686

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Signature	Sandee Whitley		
Typed or printed name	Sandee Whitley	Date	May 16, 2005

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Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of claims:

1. (Withdrawn) A particle, comprising:
   (1) a core, comprising calcium phosphate;
   (2) a therapeutic agent associated with the core; and
   (3) a layer comprising casein at least partially covering the core.

2. (Withdrawn) The particle of claim 1, wherein the therapeutic agent is selected from the group consisting of insulin, Alpha-1-Antitrypsin, Human Growth Hormone (HGH); Erythropoeitin (EPO), Steroids, drugs to treat osteoporosis, blood coagulation factors, anti-cancer drugs, antibiotics, lipase, garanulocyte-colony stimulating factor (G-CSF), Beta-Blockers, anti-asthma, anti-sense oligonucleotides, therapeutic antibodies, DNase enzyme for respiratory diseases, anti-inflammatory drugs, anti-virals, anti-hypertensives, cardiotherapeutics, anti-arrythmia drugs, gene therapies; diuretics, anti-clotting chemicals, and any combination thereof.

3. (Withdrawn) The particle of claim 1, wherein the particle size ranges from about 300 nm to about 10 microns.

4. (Withdrawn) The particle of claim 1, wherein the therapeutic agent is at least partially coated on the outside of the core, at least partially encapsulated within the core, or a combination of both.

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5. (Withdrawn) The particle of claim 1, further comprising a surface modifying agent at least partially coated on the outside of the core, at least partially embedded within the core, or a combination of both.

6. (Withdrawn) The particle of claim 5, wherein the surface modifying agent is selected from the group consisting of basic sugars, modified sugars, polyethylene glycol, cellobiose, oligonucleotides, carbohydrates, carbohydrate derivatives, macromolecules with carbohydrate-like components, and combinations thereof.

7. (Withdrawn) A therapeutic composition comprising the particle of claim 1 and a pharmaceutically acceptable excipient.

8. (Withdrawn) The therapeutic composition of claim 7, wherein the therapeutic agent is insulin.

9. (Withdrawn) A therapeutic composition suitable for oral delivery of insulin, comprising:

(1) a core comprising calcium phosphate;

(2) insulin and polyethylene glycol associated with the core; wherein the insulin and polyethylene glycol are at least partially encapsulated within the core;

(3) a capsule comprising casein at least partially covering the core;

wherein the capsule is combined with a pharmaceutically acceptable excipient.

10. (Withdrawn) A method of preparing one or more particles having calcium phosphate complexed with a therapeutic agent to form a particle, wherein the particle is encapsulated by casein, comprising:

(a) reacting a soluble calcium salt, a soluble phosphate salt, and the therapeutic agent to form a mixture;

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(b) dispersing the mixture in a solution of casein.

11. (Withdrawn) The method of claim 10, wherein the reacting (a) further comprises:

(i) mixing the therapeutic agent with a surface modifying agent; and

(ii) reacting the soluble calcium salt and the soluble phosphate salt with the therapeutic agent and surface modifying agent to form the mixture.

12. (Currently Amended) A method for delivering a therapeutic amount of a therapeutic agent to a patient in need thereof, comprising orally delivering one or more particles comprising:

(1) a core, comprising calcium phosphate;

(2) a therapeutic agent associated with the core; and

(3) a layer comprising casein at least partially covering and forming a protective coating that encapsulates the core.

13. (New) The method of claim 12, wherein the therapeutic agent is selected from the group consisting of insulin, Alpha-1-Antitrypsin, Human Growth Hormone (HGH); Erythropoeitin (EPO), Steroids, drugs to treat osteoporosis, blood coagulation factors, anti-cancer drugs, antibiotics, lipase, garanulocyte-colony stimulating factor (G-CSF), Beta-Blockers, anti-asthma, anti-sense oligonucleotides, therapeutic antibodies, DNase enzyme for respiratory diseases, anti-inflammatory drugs, anti-virals, anti-hypertensives, cardiothcrapeutics, anti-arrythmia drugs, gene therapies; diuretics, anti-clotting chemicals, and any combination thereof.

14. (New) The method of claim 12, wherein the therapeutic agent is at least partially coated on the outside of the core, at least partially encapsulated within the core, or a combination of both.

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15. (New) The method of claim 12, further comprising a surface modifying agent at least partially coated on the outside of the core, at least partially embedded within the core, or a combination of both.

16. (New) The method of claim 15, wherein the surface modifying agent is selected from the group consisting of basic sugars, modified sugars, polyethylene glycol, cellobiose, oligonucleotides, carbohydrates, carbohydrate derivatives, macromolecules with carbohydrate-like components, and combinations thereof.

17. (New) A method for delivering a therapeutic amount of insulin to a patient in need thereof, comprising orally delivering one or more particles comprising:

(1) a core comprising calcium phosphate;

(2) insulin associated with the core; wherein the insulin is at least partially encapsulated within the core, at least partially coated on the outside of the core, or a combination of both;

(3) a layer comprising casein at least partially covering and forming a protective coating that encapsulates the core.

18. (New) The method of claim 17, further comprising polyethylene glycol associated with the core.

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REMARKS/ARGUMENTS

I. Introduction

Upon entry of the present amendment, claims 12-18 will be pending in this application. Claim 12 has been amended to clarify certain aspects of the invention and claims 13-18 have been added to further define the invention. Support for the amendment and new claims appears in the specification claims as originally filed. No new matter has been added.

Because the present amendments materially reduce the issues for appeal, and place this application into better condition for allowance, entry is appropriate under 37 C.F.R. § 1.116, and is respectfully requested. Based on the following remarks, Applicants respectfully request reconsideration and allowance of the pending claims.

II. 35 U.S.C. § 103

The Examiner has rejected Claim 12 under 35 U.S.C. § 103(a) as being unpatentable over Lee et al (WO 00/15194) in view of Corrigan et al. (WO 99/03451). The Examiner's position is that it would have been obvious for one of skill in the art to use the casein disclosed by Corrigan et al. in conjunction with the calcium phosphate particles disclosed by Lee et al. in order to take advantage of the reduced gastrointestinal irritation and increased drug delivery associated with the use of casein. Applicants respectfully traverse the Examiner's rejection, request that is be reconsidered and withdrawn, and submit that the pending claims should be allowed.

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A. The Lee and Corrigan references are not properly combinable

In order to establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references when combined must teach or suggest all the claim limitations. See MPEP § 2142. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the applicant's disclosure." The initial burden is on the Examiner to provide some suggestion of the desirability in doing what the inventor has done.

The Examiner admits that the Lee reference does not disclose the use of casein as a coating substance for the calcium phosphate particles. Moreover, nowhere in the Lee reference is there any suggestion of (a) delivering the particles orally or (b) for coating the particles to prevent their degredation by digestive enzymes. Lee discusses encapsulating its calcium phosphate particles in a liposome or polymer, but that is because "liposome and polymers (e.g., PMMA, PLGA, PLA, gelatin, poly(phosphazene)), particularly biodegradable polymers, may also increase adjuvant activity by themselves serving as a delivery vehicle for the inventive calcium phosphate adjuvant." *See* Lee at page 20. Liposome drug delivery is a completely different category of drug delivery from the present invention and completely different from the drug delivery of Corrigan. Liposomes are composed of a phospholipid layer in which the phosphorus moiety is on the outside and the

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lipid moiety is on the inside. The layer encapsulates a watery liquid, not solid particles, proteins, or fatty acids. Caseins are phosphorylated proteins but they are not phospholipids.

Moreover, Lee does not disclose or suggest delivering its particles orally. Page 30 of the Lee reference describes a myriad of administration methods, including injection, surgical implantation, transdermal delivery, mucosal delivery, inhalation, and ocular administration. There is no suggestion that the treatment may be delivered orally or that it would be desirable to provide a way for such a delivery. Accordingly, one or ordinary skill in the art would not be motivated to coat the Lee particles with the casein described by the Corrigan reference, which is directed to a way to prevent gastrointestinal irritation due to delivery of drugs that have gastrointestinal irritating effects, to provide for oral delivery of the Lee particles. There is simply no teaching in either reference that suggests such a combination.

B. Even if the references were combinable, the claimed invention would not result

Even if the Lee and Corrigan references were combined, the presently-claimed invention would not result. The Lee particles are different from Applicant's particles, and the Corrigan reference discloses the use of casein in pharmaceutical compositions to reduce the irritating effects of the active ingredient. Corrigan specifically indicates that its invention is for use with active ingredients that have gastrointestinal irritating effects. *See* page 5. Its particles are made by mixing and compression, granulation processes, spray drying of freeze drying the components together. By contrast, Applicants' particles are produced by reconstructing casein micelles around therapeutic agent-loaded CAP particles for the purpose of creating a protective coat surrounding the CAP-therapeutic agent particles. Neither

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Corrigan or Lee nor their combination disclose a calcium phosphate core, a therapeutic agent associated with the core; and a layer comprising casein at least partially covering and forming a protective coating that encapsulates the core, as presently claimed. Because the references, alone or in combination, do not teach or suggest each limitation of claims 12-18, Applicants respectfully request reconsideration of the current rejections and reconsideration thereof.

CONCLUSION

For at least the above reasons, Applicant respectfully requests allowance of claims 12-18 and issuance of a patent containing these claims in due course. If there remain any additional issues to be addressed, the Examiner is urged to contact the undersigned attorney at 404.815.6147.

Respectfully submitted,

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